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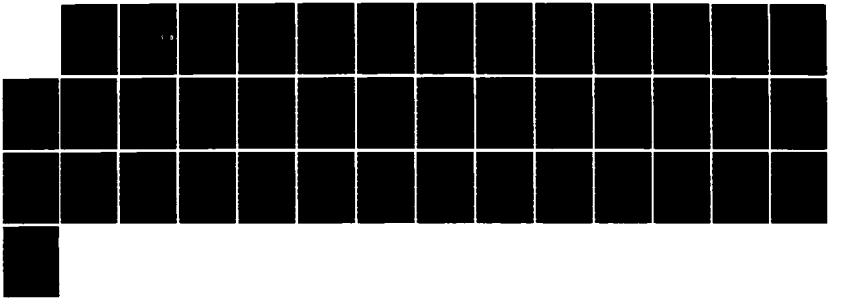

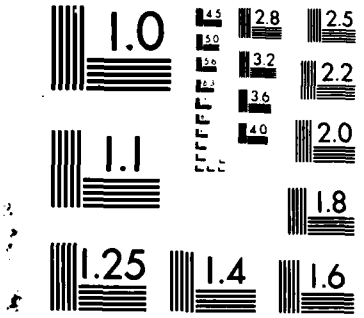

EVIDENCE FOR PERIPHERAL TISSUE DIFFUSION LIMITATION OF MAXIMUM O_2 UPTAKE

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Maximum oxygen uptake(VO_2 max) is often said to be limited by blood O2 transport at sea level and by pulmonary diffusion disequilibrium at altitude. Neither of these mechanisms directly addresses the role of peripheral tissue O2 extraction. A retrospective analysis of directly measured mixed venous PO_2 (PVO2) during exercise at both sea level and simulated altitude in 15 normal subjects revealed that PVO2 at VO_2 max was very different at sea level compared to altitude. While even at submaximal workloads PVO2 at altitude readily fell below 20 torr, even at maximal workloads it remained at or above 20 torr at sea level in spite of a much higher VO2 max at sea level. Moreover, the relationship between VO2 max and PVO_2 was linear through the origin in all subjects. On the assumption that at VO_2 max, average effluent muscle capillary PO_2 is proprotional to PVO_2, these data are compatible with the notion of tissue diffusion limitation of VO_2 max. This argument is based on Fick's 1st law of diffusion further assuming that at VO_2 max, mitochondrial PO2 is sufficiently close to zero to be negligible. Thus, one would predict that VO2 max is linearly dependent on the head of pre-

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ssure (PO_2)in the muscle cappillary and by altering this PO_2 during altitude simulation, such linearity was demonstrated. Perhaps surprisingly, we found no difference in the PVO2/ VO_2 max relationship at altitude according to whether altitude exposure was acute or chronic. We suggest that: 1) VO_2 max at any altitude is limited by peripheral tissue O_2 diffusion between the capillary and the mitochondrion, 2) at any particular altitude, O_2 delivery will set the actual VO_2 max depending on the diffusing capacity of the tissues, with O_2 delivery depending in turn on cardiac output, hemoglobin concentration and arterial O_2 saturation.

ABSTRACT

Maximum oxygen uptake ($\dot{V}O_{2max}$) is often said to be limited by blood O_2 transport at sea level and by pulmonary diffusion disequilibrium at altitude. Neither of these mechanisms directly addresses the role of peripheral tissue O_2 extraction. A retrospective analysis of directly measured mixed venous PO_2 ($P\bar{v}O_2$) during exercise at both sea level and simulated altitude in 15 normal subjects revealed that $P\bar{v}O_2$ at $\dot{V}O_{2max}$ was very different at sea level compared to altitude. While even at submaximal workloads $P\bar{v}O_2$ at altitude readily fell below 20 torr, even at maximal workloads it remained at or above 20 torr at sea level in spite of a much higher $\dot{V}O_{2max}$ at sea level. Moreover, the relationship between $\dot{V}O_{2max}$ and $P\bar{v}O_2$ was linear through the origin in all subjects. On the assumption that at $\dot{V}O_{2max}$, average effluent muscle capillary PO_2 is proportional to $P\bar{v}O_2$, these data are compatible with the notion of tissue diffusion limitation of $\dot{V}O_{2max}$. This argument is based on Fick's 1st law of diffusion further assuming that at $\dot{V}O_{2max}$, mitochondrial PO_2 is sufficiently close to zero to be negligible. Thus, one would predict that $\dot{V}O_{2max}$ is linearly dependent on the head of pressure (PO_2) in the muscle capillary and by altering this PO_2 during altitude simulation, such linearity was demonstrated. Perhaps surprisingly, we found no difference in the $P\bar{v}O_2/\dot{V}O_{2max}$ relationship at altitude according to whether altitude exposure was acute or chronic. We suggest that: 1) $\dot{V}O_{2max}$ at any altitude is limited by peripheral tissue O_2 diffusion between the capillary and the mitochondrion, 2) at any particular altitude, O_2 delivery will set the actual $\dot{V}O_{2max}$ depending on the diffusing capacity of the tissues, with O_2 delivery depending in turn on cardiac output, hemoglobin concentration and arterial O_2

saturation.

Key words: maximal O_2 consumption
exercise
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INTRODUCTION

The steps that result in delivery of environmental O_2 to the mitochondria for energy generation are well-known. Alveolar ventilation delivers O_2 to the alveolar blood:gas barrier across which O_2 then diffuses and combines with hemoglobin. Blood containing O_2 is convected to the tissues where diffusional processes transport O_2 from the red cell to the intracellular sites of utilization. For many years there has been interest in how these linked processes function at maximum O_2 consumption ($\dot{V}O_{2max}$), and especially which component might be the rate-limiting step that sets the upper limit on $\dot{V}O_2$. There seems to be a general consensus that convective transport to the tissues by blood is the rate-limiting step in man at sea level (4,11). However, others have suggested that it is not any component of the delivery system but rather that $\dot{V}O_{2max}$ is the result of maximal biochemical function of the mitochondrial energy generation system: Even if more O_2 could be supplied, it could not be used (9,10). Still others have suggested a role for the central nervous system, especially at altitude. This is based on observations that at altitude (unlike sea level), muscle biopsies show little glycogen depletion at $\dot{V}O_{2max}$ (3).

The concept of a single rate-limiting process in determining $\dot{V}O_{2max}$ seems dissatisfying, however, at any metabolic rate less than that associated with true maximum biochemical utilization of O_2. It seems entirely possible that at less than full mitochondrial function, measured $\dot{V}O_{2max}$ could be raised by increasing the number of O_2 molecules delivered to the muscle per unit time. This in turn could be achieved by any factors that augment the

value of muscle O_2 delivery defined as the product of muscle bloodflow and arterial O_2 content. Potential factors include increases in bloodflow, hemoglobin concentration, arterial O_2 saturation and O_2 partial pressure.

Another phenomenon that seems to have received relatively little attention is the inability to completely extract O_2 from blood, even at $\dot{V}O_{2max}$. Only a few measurements of femoral venous or mixed venous PO_2 have been made at $\dot{V}O_{2max}$, and while such PO_2's are low, they are not zero, and may be substantial. Thus, Pirnay et al. (10) noted that femoral venous PO_2 did not fall below 17 torr while Andersen and Saltin (1) found femoral venous PO_2 did not fall below 24 torr (sea level measurements); we found mixed venous PO_2 measured at 80-90% of $\dot{V}O_{2max}$ and extrapolated to $\dot{V}O_{2max}$ was about 20 torr (16) at sea level.

The key observation that led to the analysis in this paper is shown in figure 1 and pertains to mixed venous PO_2 at several values of $\dot{V}O_{2max}$. This figure illustrates for one normal subject, mixed venous PO_2 at several values of $\dot{V}O_2$, both at sea level and at simulated altitude (PB=347 torr). Equivalent altitude was 20,000 feet or 6096 m. Note that PvO_2 is much higher at sea level than at altitude and simultaneously $\dot{V}O_{2max}$ is also much higher at sea level. In fact, PvO_2 and $\dot{V}O_{2max}$ are essentially linearly related to one another by a line through the origin. In addition, $\dot{V}O_{2max}$ results in extraction of O_2 to different degrees at sea level compared to altitude. Importantly, extraction is not complete at either altitude. Based on those observations (confirmed in a total of 15 subjects), we offer the following analysis of how $\dot{V}O_{2max}$ may be determined.

ANALYSIS

Consider a vessel supplying a small region of skeletal muscle. For purposes of simplicity we ignore metabolism: bloodflow inequality throughout the muscle, and further consider all of the O_2 leaves the capillary at a single point spatially. It seems logical that these simplifications, used only for presentation purposes, can be removed later without altering the hypothesis.

The analysis is based on the concept of mass balance between capillary O_2 unloading (Fick principle), and tissue diffusion of O_2 from the capillary to the mitochondrion, (Fick's first law of diffusion). O_2 uptake by Fick principle is stated by the well-known relation:

$$\dot{V}O_2 = \dot{Q}[CaO_2 - CvO_2] \qquad (1)$$

where $\dot{Q}$ is muscle bloodflow and CaO_2 and CvO_2 are O_2 contents of inflowing and effluent muscle capillary blood respectively.

Subsequent diffusion from the capillary to the mitochondrion can simply be expressed as

$$\dot{V}O_2 = DO_2 [PvO_2 - P_{mitO2}] \qquad (2)$$

where DO_2 is some lumped parameter value of total conductance ("diffusing capacity") for O_2 over the complex pathway from the hemoglobin molecule in the red cell all the way to the mitochondrial site of utilization.

We will further assume that at $\dot{V}O_{2max}$, mitochondrial PO_2 is sufficiently low that it can be neglected, an assumption that appears reasonable (8).

Equation (2) then becomes

$$\dot{V}O_2 = DO_2 \cdot PvO_2 \qquad (3)$$

Under steady state conditions, equations (1) and (3) must reflect the same quantities of O_2 being delivered per unit time. This mass conservation principle then leads to:

$$\dot{V}O_2 = Q[CaO_2 - CvO_2] = DO_2 \cdot PvO_2$$

Figure 2 plots $\dot{V}O_2$ both from equation (1) and equation (3) as a function of effluent venous PO_2. For equation (1), as PvO_2 increases from 0 to its hypothetical maximum value of inflowing arterial PO_2, $\dot{V}O_2$ will progressively fall towards zero. The relationship will be approximately linear because in the normal range of PvO_2 at $\dot{V}O_{2max}$, PO_2 is on the steep, almost linear part of the O_2 Hb dissociation curve. For equation (3), the relationship between $\dot{V}O_2$ and PvO_2 is quite the opposite of that in equation (1): it is a straight line through the origin whose slope is the numerical value of the tissue O_2 conductance term DO_2 in equation (3). In words, the higher the effluent venous PO_2 (for a given bloodflow and arterial O_2 content), the lower will be $\dot{V}O_2$ calculated by Fick principle and the higher will be $\dot{V}O_2$ calculated by Fick's law of diffusion.

The point of intersection gives $\dot{V}O_{2max}$. Thus, at any lower PvO_2, the Fick principle would allow a greater $\dot{V}O_2$ through greater extraction, but this could not in fact be realized because any lower PvO_2 could not support transport of O_2 by diffusion from the capillary to the mitochondrion. Any higher PvO_2 (than at the point of intersection of the two lines of figure 2)

could support a higher $\dot{V}O_2$ in terms of tissue diffusion but such a higher $\dot{V}O_2$ would not occur because the higher PvO_2 must per se be associated (equation (1)) with a lower actual $\dot{V}O_2$.

Figure 2 lends itself to further analysis. At any other muscle bloodflow, similar geometric expressions of equations (1) and (3) could be drawn, or alternatively for a given muscle bloodflow and arterial O_2 content, the relationships can be constructed for a muscle whose O_2 diffusive conductance (DO_2) is different.

For a different bloodflow (but unchanged arterial O_2 content and DO_2), effluent muscle PO_2 and $\dot{V}O_{2max}$ would both change in the same direction as muscle bloodflow. Furthermore, the relationship between PvO_2 and $\dot{V}O_{2max}$ will remain constrained by the same equation (equation (3)) as long as DO_2 is not altered by bloodflow. It is also easy to see how a change in arterial O_2 content will have qualitatively the same effect on PvO_2 and $\dot{V}O_{2max}$ as will a change in muscle bloodflow (equation (3)).

The relationship between PvO_2 and $\dot{V}O_{2max}$ would be altered differently if DO_2 were to increase. An increase in $\dot{V}O_{2max}$ would be possible (at constant cardiac output and arterial O_2 content) while at the same time, PvO_2 would fall.

Figure 3 shows an extension of figure 2 to include a consideration of the effects of high altitude exposure causing a reduction in CaO_2. In particular, it shows the linear relationship to be expected between $\dot{V}O_{2max}$ and PvO_2 at different altitudes. The major assumption of figure 3 is lack of change in DO_2 with altitude.

Examination of experimental data. The hypothesis of tissue diffusion limitation of $\dot{V}O_{2max}$ was developed in retrospect after examining data from two studies in which $P\bar{v}O_2$ at or near $\dot{V}O_{2max}$ was measured in 15 normal subjects (15,16). The purpose of these two studies was to examine pulmonary gas exchange rather than peripheral tissue events, and so the experimental design was not specifically formulated to test the hypothesis of peripheral tissue diffusion limitation. These studies have been described in detail and all that is needed from them are the values of mixed venous PO_2 and $\dot{V}O_{2max}$ in each subject at each exercise level. In both studies, simultaneous measurements of $\dot{V}O_2$ and $P\bar{v}O_2$ were made at rest and at several levels of steady state exercise up to 80-90% of $\dot{V}O_{2max}$, both at sea level and several simulated altitudes.

The first study (8 subjects) was an acute 1-day exposure to altitude (PB=429 torr and 523 torr or 15,000 feet and 10,000 feet equivalent altitudes respectively). It was done at Duke University in late 1983 (16). The second (7 subjects), referred to as Operation Everest II (OE II) (15), involved gradual simulated ascent to PB=240 torr equivalent in PIO_2 to the summit of Mount Everest. In that study, data pertinent to the current paper were obtained at sea level and pressures of 347, 282 and 240 torr equivalent to 20,000, 25,000 and 29,000 feet above sea level (6096, 7620 and 8840 meters respectively). The relevant data appear in Tables I and II.

In both cases, mixed venous PO_2 was measured in blood samples drawn from an indwelling pulmonary artery catheter using conventional blood:gas electrodes. Oxygen uptake was measured by expired gas analysis using either a dry gas meter (15) or a Tissot spirometer (16) for ventilation and a mass

spectrometer (15) or gas chromatograph (16) for mixed expired O_2 and CO_2 concentrations. Close attention was paid to ensuring steady state conditions at all exercise loads which were set to achieve $\dot{V}O_2$ values of 80-90% of $\dot{V}O_{2max}$ (15) or a heart rate of about 175 min^{-1} (16). Only in OE II was true $\dot{V}O_{2max}$ measured (15), and mixed venous PO_2 could thus be extrapolated to that value. $\dot{V}O_{2max}$ was obtained on a separate occasion from when $P\bar{v}O_2$ was measured (but at each altitude in which the studies measuring $P\bar{v}O_2$ were conducted). In the acute altitude exposure study, given the high heart rates and lack of formal $\dot{V}O_{2max}$ measurement, we have used the data assuming that at each altitude, the actual greatest $\dot{V}O_2$ achieved was a constant fraction of true $\dot{V}O_{2max}$. Except for two specific occasions (Table I), we suggest that this is reasonable based on heart rate data and that any deviation from this assumption is probably a small random factor. If this assumption is true, linearity of the relationship between $P\bar{v}O_2$ and greatest $\dot{V}O_{2max}$ would still be expected although the slope of that relationship would not reflect the true value of DO_2: this estimate of tissue DO_2 would be systematically low, close to the same percentage as was the actual highest $\dot{V}O_2$ to $\dot{V}O_{2max}$ (different by about 8%, Table I). Two specific measurements were not used (Table I) because of clear-cut evidence of failure to achieve near-maximal heart rates. These were the PB=429 torr studies in subjects ML and DM.

RESULTS

Figures 4 and 5 present the entire set of relationships between measured mixed venous PO_2 and measured $\dot{V}O_2$ for both studies. Figure 4 represents acute altitude exposure while figure 5 refers to OE II. In figure 5 the

measured relationships are extrapolated to the independently measured values of $\dot{V}O_{2max}$. Such extrapolations were done by hand and are seen to be generally of minor proportions.

It is remarkable that in all subjects the data lie close to a straight line through the origin. While all data in figure 4 fit the hypothesis well, figure 5 shows a curious systematic difference. The data at sea level, PB=347 torr and PB=282 torr fit extremely well, but this is not the case at the "summit" (PB=240 torr) in all 4 subjects in whom measurements were possible.

Figures 4 and 5 also show that the slopes of the $P\bar{v}O_2/\dot{V}O_{2max}$ relationships vary considerably amongst the subjects of both studies. It is evident that those subjects with the lowest slopes (highest "DO_2") also have the highest $\dot{V}O_{2max}$ values. Even though "DO_2" is determined by the ratio of $\dot{V}O_{2max}$ to minimum $P\bar{v}O_2$, figures 4 and 5 indicate that there need not be any a priori relationship between "DO_2" and $\dot{V}O_{2max}$. Thus it might have transpired, for example, that because of a lower cardiac output, $\dot{V}O_{2max}$ may have been lower but DO_2 could still have remained high. Figure 6 shows the relationship between "DO_2" and $\dot{V}O_{2max}$ (or greatest $\dot{V}O_2$ reached for the subjects of figure 4) and while $\dot{V}O_{2max}$ does appear on both axes, there need not be such a clear relationship as figure 6 shows, as was argued above.

A more independent pair of variables is plotted in figure 7 to show the relationship between mixed venous PO_2 (at $\dot{V}O_{2max}$) and $\dot{V}O_{2max}$ amongst all subjects at sea level. There is a clear correlation (r=0.62) between the two, such that a higher $\dot{V}O_{2max}$ for any given subject is associated with a lower mixed venous PO_2.

DISCUSSION

Assumptions. In considering the merits of this paper and its central hypothesis of tissue diffusion limitation of $\dot{V}O_{2max}$, it should be remembered that the reported data were obtained before the hypothesis was ever conceived. Consequently, there are many assumptions and implications that, if not acceptable, may well refute the concept, and these should be presented to provide a foundation for any future work in this area. Perhaps the most important assumption is that of proportionality between mixed venous and effluent muscle capillary PO_2. Note that equivalence is not necessary (because of Fick's law requiring that the $\dot{V}O_{2max}/P\bar{v}O_2$ relationship pass through the origin). Further, proportionality is required only at $\dot{V}O_{2max}$, at which $\dot{V}O_2$ the hypothesis is directed. We feel that the assumption is reasonable because of the extremely high cardiac output under most of the conditions that provided data for figures 4 and 5. Thus, cardiac output at $\dot{V}O_{2max}$ was about 24 L/min throughout the acute altitude project (16) and at sea level, PB=347 and 282 torr, also in excess of 20 L/min in OE II. In fact, one possible explanation of the anomalous result at the summit (PB=240 torr) in OE II may be that because $\dot{V}O_{2max}$ is low, so is cardiac output. While about 80-90% of the cardiac output of >20 L/min at sea level and intermediate altitudes must be perfusing exercising muscle, a considerably lower fraction will be devoted to muscle at the lower cardiac ouput on the "summit". Thus the blood returning from all tissues other than muscle contaminates returning muscle blood only to approximately 10-20%, except on the summit where the contamination was probably greater (assuming 4 L/min perfusing non-exercising tissues).

Perhaps the most direct and feasible approach to testing the assumption of proportionality between mixed venous and effluent muscle venous PO_2 would be to sample femoral venous and mixed venous blood simultaneously under all of the conditions of our studies. The literature was surprisingly found not to contain data of this type, and future evaluation of the diffusion limitation hypothesis must clearly examine femoral venous PO_2, even if some of that blood is derived from skin perfusion.

A second assumption is that in the acute altitude studies (figure 4) subjects reached a more or less constant fraction of $\dot{V}O_{2max}$ at the highest workload during which data were obtained at each altitude. Again, because of Fick's law of diffusion, a constant fraction of rather than equivalence to $\dot{V}O_{2max}$ is sufficient. Evidence supporting this assumption and also indicating how close each subject was to $\dot{V}O_{2max}$ (at sea level) came from heart rate data (Table 1) where the mean was 177±7 SD. $\dot{V}O_{2max}$ was estimated for each subject at sea level (Table 1) and the highest measured $\dot{V}O_2$ values expressed as a percentage of this estimate average 93±7 SD. Finally, heart rates at sea level, 10,000 feet and 15,000 feet averaged 177, 177 and 174 min^{-1} respectively (excluding at 15,000 feet 2 subjects (ML and DM) who clearly did not reach heart rates close to their prior values at sea level or 10,000 feet). Taken together, these data support the use of these values as being very close to those expected at $\dot{V}O_{2max}$.

A third assumption pertains to steady state conditions necessary for equivalence of equations (1) and (3) in expressing $\dot{V}O_2$. In all subjects from both studies the data for this analysis were collected between the 3rd and 6th minutes of exercise at the heaviest workloads and between 5 and 10

minutes of exercise at lighter loads. Over these time periods, respiratory frequency, minute ventilation and heart rate were all constant to ±5%, and thus for the purposes of this analysis, a sufficiently steady state existed. Twenty second averages of $\dot{V}O_2$ obtained from expired gas analysis by computer in OE II (12) showed no systematic variation in $\dot{V}O_2$ during these time periods. End-tidal PO_2 and PCO_2 signals were constant to +5% in the subjects from the acute altitude exposure study (16), but not measured in OE II.

A fourth assumption is that mitochondrial PO_2 is sufficiently close to zero that it can be neglected in equation (3). This is supported by data in the literature (8).

Finally, an implicit assumption of the foregoing analysis (but certainly not necessary for the hypothesis of tissue diffusion limitation itself) is that the effective diffusive conductance, DO_2 of equation (3), is constant for any one subject amongst the various altitudes. It is certainly conceivable that acute altitude exposure (hypoxia) could alter vascular tone and thus potentially alter intercapillary distances and hence result in different "DO_2" values from those at sea level. While this can probably be examined only by direct morphometric measurement at various altitudes, it is unlikely to be a factor at $\dot{V}O_{2max}$. We feel it more reasonable that at $\dot{V}O_{2max}$, irrespective of ambient PO_2, all working muscle vessels are fully dilated. An interesting issue does arise, however, for the subjects in OE II where extreme altitude was attained gradually over 40 days (15). It is possible that structural tissue adaptations such as reduction in muscle fiber size (2) and/or increased capillarity (13) occur to reduce intercapillary distances. The experiments performed in OE II do not directly address this

issue in a form pertinent to the current analysis: the best way to examine this possibility would be to study the same subjects (along the lines of this analysis) both after acute and after chronic altitude exposure. Tissue adaptation would be expected to result in an increased value for "DO_2" (i.e. a higher $\dot{V}O_{2max}$ at a lower capillary PO_2), and this could be directly tested by such an experiment. Until then, such considerations must remain speculative.

Alternative hypotheses. The observation that at $\dot{V}O_{2max}$ mixed venous PO_2 (and presumably effluent muscle venous PO_2) is considerably lower at altitude than at sea level (Tables I and II) despite much higher values of VO_{2max} at sea level is difficult to explain other than by the hypothesis of this paper. One possible alternative is that biochemical utilization of O_2 is truly at its maximum at sea level, and that additional O_2, even if available could not be used. Evidence against this explanation comes from reported increases in $\dot{V}O_{2max}$ while breathing elevated O_2 concentrations. This controversial area was reviewed by Welch (17) and despite difficulties of a technical nature in measuring $\dot{V}O_2$ breathing high O_2 concentrations, 14 of 15 published studies reported an increase in $\dot{V}O_{2max}$ of 2-19% breathing gases of FIO_2 of 0.33 to 1.00 at sea level and also in hyperbaric studies. Further evidence against a biochemical limit to sea level $\dot{V}O_{2max}$ comes from studies in which hemoglobin concentration is acutely altered (4,7,14,20), whereby $\dot{V}O_{2max}$ increases and decreases in the same direction as hemoglobin levels.

The possibility that effluent muscle venous PO_2 is higher at sea level because of O_2 diffusion disequilibrium in the muscle capillary during unloading appears to require a reduced transit time as its basis. That

cardiac output was no higher at VO_{2max} at sea level compared to altitude in our subjects with acute altitude exposure (16) argues against this hypothesis.

Data at the simulated summit of Mount Everest. Figures 4 and 5 are remarkable for their consistency with the diffusion limitation hypothesis, except at PB=240 (Everest summit PIO_2) in the OE II experiment. It is difficult to explain the discrepancy. Maximum mean measured cardiac output in subjects 1,3 and 4 was 17.3 L/min at PB=282 and 18.0 L/min at PB=240. $\dot{V}O_{2max}$ for those three subjects at these altitudes were 1.86 L/min and 1.07 L/min respectively. One explanation could be that the subjects were not truly at $\dot{V}O_{2max}$ on the summit. The conditions were rather hectic and ensuring as good quality of measurement as at lower altitudes had to come second to concerns for the subjects' safety and comfort. Another possibility is some other dominant factor limiting performance at the summit (e.g. central nervous system influences unrelated to metabolic variables such as PO_2). While no clear answer can presently be given, the bulk of the measurements in the 15 subjects of both studies still fit the diffusion limitation hypothesis and further measurements under extreme hypoxia will be required to resolve the discrepancy on the summit.

Limitation of $\dot{V}O_{2max}$ at sea level and simulated altitude. As stated in the introduction, most physiologists appear to have concluded that O_2 delivery is the principal factor limiting $\dot{V}O_{2max}$ at sea level (4,11), while at altitude, pulmonary diffusion limitation becomes the critical factor (6,18).

This paper proposes a somewhat different view of what limits $\dot{V}O_{2max}$. The central factor at <u>any</u> altitude is the capacity to transport O_2 by diffusion from the muscle capillary to the mitochondrion. The secondary factor is O_2 delivery (which is itself the product of the three principal terms: cardiac output, hemoglobin concentration and arterial O_2 saturation (ignoring dissolved O_2)). We propose that at any value of O_2 delivery, $\dot{V}O_{2max}$ is limited by tissue diffusion of O_2 from the red cell to the mitochondrial site of utilization. Specifically (as shown in figure 2), $\dot{V}O_{2max}$ is determined by the balance between what can be unloaded from blood as described by the Fick principle, and what can subsequently be transported to the mitochondrion by diffusion.

Any event that increases O_2 delivery (increased cardiac output, hemoglobin concentration or arterial O_2 saturation/PO_2) will increase $\dot{V}O_{2max}$. Equations (1) and (3) can be equated and solved to predict just how much increase in $\dot{V}O_{2max}$ is to be expected from a given change in O_2 delivery.

Finally, the relationship between O_2 delivery, $\dot{V}O_{2max}$ and effluent venous PO_2 can be altered by functional and/or structural tissue adaptations to, for example, exercise or chronic altitude exposure. Such alterations in "DO_2" would alter $\dot{V}O_{2max}$ for a given O_2 delivery in ways predictable from equations (1) and (3).

<u>Extension to the concept of critical PO_2</u>. In concept, the hypothesis of this paper fits the observation of a critical PO_2 (in the resting state) above which $\dot{V}O_2$ is independent of O_2 delivery and below which $\dot{V}O_2$ is proportional to O_2 delivery (5) as shown in figure 8. Suppose in reference to figure 8 a particular value of tissue DO_2 exists, thus leading to the line

through the origin having positive slope and describing Fick's law of diffusion (compare figure 2). Also in figure 8, a nubmer of lines of negative slopes are drawn expressing $\dot{V}O_2$ by the Fick principle as a function of venous PO_2. Each line represents the allocation of a different cardiac output but constant CaO_2. Assume resting $\dot{V}O_2$ is as marked by the dashed horizontal line. Where that dashed line intersects the $DO_2 \times P\bar{v}O_2$ line, yields the critical $P\bar{v}O_2$: at higher $P\bar{v}O_2$ values (occurring with higher cardiac output values) diffusional transport is more than sufficient to accomodate resting $\dot{V}O_2$. However, below critical $P\bar{v}O_2$, diffusional transport capability is less than resting $\dot{V}O_2$ and so actual $\dot{V}O_2$ (solid circles) must fall (and lie along the $DO_2 \times P\bar{v}O_2$ line) as $P\bar{v}O_2$ falls due to further reductions in cardiac output. This analysis is compatible with the work of Willford et al. (19) and extends the hypothesis from $\dot{V}O_{2max}$ down to resting conditions.

Future applications. Should the tissue diffusion limitation hypothesis be borne out by future work, diagrams such as figures 1, 4 and 5 might be useful in analyzing adaptation to exercise or altitude. One could envisage determining the $\dot{V}O_{2max}/P\bar{v}O_2$ relationship prior to, and several weeks after an exercise training program, or a sojourn at altitude. In each case, this relationship requires measuring mixed venous or femoral PO_2 at $\dot{V}O_{2max}$ at sea level and at perhaps two values of reduced inspired PO_2. Possible outcomes and their interpretation are given in figure 9. One possible response of a subject after exercise training might be to move further up the original $\dot{V}O_{2max}/P\bar{v}O_2$ relationship (to point A, figure 9 from the starting point 0),

which would be interpreted as an improvement in $\dot{V}O_{2max}$ produced by augmented O_2 delivery but without change in effective diffusing conductance for O_2 at the tissues. Another alternative might be to move from point O to point B on a new $DO_2/P\bar{v}O_2$ line. The necesary inference is that $\dot{V}O_{2max}$ was enhanced by a combination of increased O_2 delivery and increased tissue conductance. Yet another possibility is movement from O to C, and this would reflect an increase in tissue conductance with no augmentation of O_2 delivery. In all three cases in this specific illustration, $\dot{V}O_{2max}$ has been increased by the same amount, and it becomes possible to determine the individual contributions of O_2 delivery and of tissue conductance to such increases.

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TABLE I. Acute altitude exposure. (Duke University study)

	Sea level, n=8				P_B=523, torr n=8			P_B=429, torr n=6		
Subject	Predicted $\dot{V}O_{2max}$ L/min	Highest $\dot{V}O_2$ L/min	Lowest $P\bar{v}O_2$ torr	Highest Hr. min^{-1}	Highest $\dot{V}O_2$ L/min	Lowest $P\bar{v}O_2$ torr	Highest Hr. min^{-1}	Highest $\dot{V}O_2$ L/min	Lowest $P\bar{v}O_2$ torr	Highest Hr. min^{-1}
ML	4.88	3.91	21	165	2.74	18	162	(1.25)*	(20)*	(133)
JG	3.17	2.89	24	183	2.42	21	190	1.75	16	176
BS	4.55	4.59	20	177	3.20	17	171	2.66	13	170
DM	2.54	2.20	27	170	1.50	21	163	(0.91)*	(18)*	(154)
RR	3.62	3.44	20	185	2.94	17	190	2.44	14	181
LM	2.08	2.08	21	173	2.13	16	181	1.35	14	168
TR	3.51	3.49	23	183	3.31	20	185	2.16	17	174
KS	3.60	3.16	15	182	2.68	13	173	2.26	9	172
Mean	3.49	3.22	21.4	177	2.62	17.9	177	2.10	13.8	174
SD	0.93	0.84	3.5	7	0.59	2.7	11	0.48	2.8	5

*Data not used because of low heart rates suggesting failure to achieve $\dot{V}O_{2max}$.

TABLE II. Chronic altitude exposure (OE II).

	SL (n=7)		P_B=347 (n=6)		P_B=282 (n=5)		P_B=240 (n=4)	
#	Measured $\dot{V}O_{2max}$	Extrapolated $P\bar{v}O_2$ at $\dot{V}O_{2max}$	Measured $\dot{V}O_{2max}$	Extrapolated $P\bar{v}O_2$ at $\dot{V}O_{2max}$	Measured $\dot{V}O_{2max}$	Extrapolated $P\bar{v}O_2$ at $\dot{V}O_{2max}$	Measured $\dot{V}O_{2max}$	Extrapolated $P\bar{v}O_2$ at $\dot{V}O_{2max}$
1	4.22	21	2.19	12	1.99	11	1.02	14
3	3.37	22	2.05	12	1.76	11	0.96	20
4	4.37	18	(2.23)	--*	1.83	6	1.24	10
5	3.55	22	1.77	13	(1.54)	--	--	--**
6	4.20	17	2.45	11	1.88	7	1.39	15
8	4.48	19	2.12	11	1.81	8	(1.25)	--+
9	3.06	26	1.60	12	(1.61)	--	--	--+
$\bar{X}$	3.89	20.7	2.03	11.8	1.85	8.6	1.15	14.8
SD	0.56	3.0	0.30	0.8	0.09	2.3	0.20	4.1

* Swan-Ganz catheter could not be inserted.

** Subject removed from chamber prior to measurement at P_B=282 and 240 torr. + subjects declined catheterization.

$\dot{V}O_{2max}$ in L/min; $P\bar{v}O_2$ in torr.

FIGURE LEGENDS

Figure 1. Relationship between measured mixed venous PO_2 and measured oxygen uptake at sea level and altitude (P_B=347 torr). Closed circles represent submaximal data and open circles extrapolations to measured maximum $\dot{V}O_2$. At maximum $\dot{V}O_2$, mixed venous PO_2 is much less at altitude than at sea level, and both points lie on a straight line through the origin, the significance of which is explained in the text.

Figure 2. Graphical analysis of the relationship between convective unloading of oxygen from the muscle capillary (Fick principle) and diffusional transport of oxygen from the red cell to the mitochondrion (expressed by Fick's law of diffusion). These two expressions for oxygen transport can be represented by essentially straight lines on a diagram relating oxygen uptake to effluent muscle capillary PO_2. The line with a negative slope expresses the Fick principle, while that with a positive slope, Fick's law. The point of intersection determines maximum $\dot{V}O_2$ as explained in the text. At $\dot{V}O_{2max}$, mitochondrial PO_2 is assumed to be sufficiently close to zero as to be negligible for the purposes of this analysis.

Figure 3. Extension of the relationship between the Fick principle and Fick's law to conditions of altitude as well at sea level. The principle effect of altitude is to reduce arterial oxygen concentration which reduces the ordinate intercept of the Fick principle line as shown. For the same "DO_2", the point of intersection of the Fick principle and Fick law lines is

lower at altitude than at sea level. It is evident that one would expect a linear relationship through the origin between maximum oxygen uptake and effluent muscle capillary PO_2.

Figure 4. Data for 8 subjects showing the relationship between measured mixed venous PO_2 and measured oxygen uptake obtained during acute altitude exposure in the Duke University study referred to in the text. Data reflect sea level conditions (SL) and barometric pressures of 523 and 428 torr. Small solid circles are data at submaximal work rates, while the large symbols reflect the highest work rates and lowest mixed venous PO_2 values achieved. As shown in Table I, these reflect greater than 90% of predicted $\dot{V}O_{2max}$ on average. Notice that for each subject the data lie close to a line through the origin. Notice also that the slope of this line varies greatly amongst different subjects, reflecting different values of apparent tissue diffusing capacity.

Figure 5. Similar plots to those in figure 4 for chronic altitude exposure as observed in Operation Everest II (OE II). Data are shown for sea level, and barometric pressures of 347, 282 and 240 torr. Except at 240 torr, the relationship between mixed venous PO_2 and oxygen uptake at maximum $\dot{V}O_2$ is linear as in figure 4. Again, the slopes of the linear relationship vary amongst the 7 subjects, indicating different levels of tissue diffusing capacity.

Figure 6. Relationship between maximum $\dot{V}O_2$ and the calculated tissue diffusing capacity for both the acute (Duke) and chronic (OE II) altitude exposure studies. A good correlation is seen, and there is no difference between acute and chronic exposure apparent. This figure shows that subjects with a higher maximum oxygen consumption also have a higher tissue diffusing capacity.

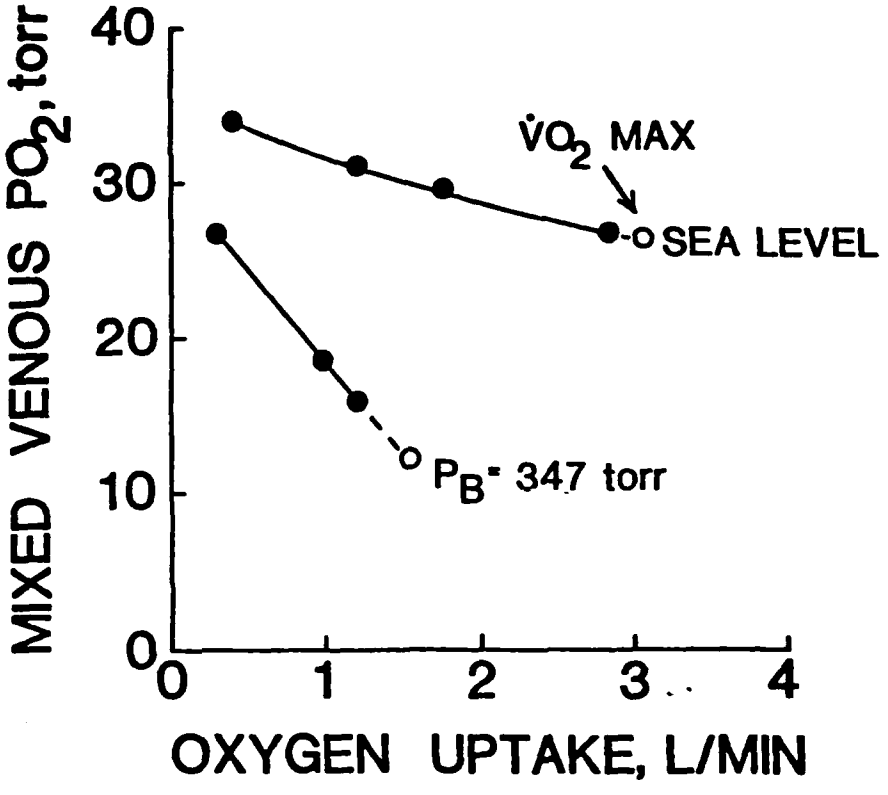
Figure 7. Relationship between maximum VO_2 at sea level and mixed venous PO_2 at maximum $\dot{V}O_2$ for the subjects from OE II (solid circles). Open circles reflect the Duke data which were obtained at an average of 93% of $\dot{V}O_{2max}$. Although the relationship is not strong, those subjects with a higher $\dot{V}O_{2max}$ had a lower mixed venous PO_2. There was no apparent difference in this relationship between the two studies.

Figure 8. Theoretical explanation for the concept of the critical PO_2, based on the same hypothesis as used to explain maximum oxygen consumption. As explained more fully in the text, at venous PO_2's (and thus oxygen deliveries) above the critical PO_2, tissue diffusing capacity is more than sufficient to meet the demands of resting $\dot{V}O_2$. Below the critical PO_2, tissue diffusing capacity is insufficient to deliver the oxygen required by resting metabolism (horizontal dashed line) and thus actual oxygen uptake must fall along the diffusing capacity line. The sequence of solid circles shows the relationship between actual $\dot{V}O_2$ and venous PO_2 as oxygen delivery is progressively reduced from right to left. Thus, the diffusion limitation hypothesis of $\dot{V}O_{2max}$ can also be used to explain the development

of a critical PO_2 when oxygen delivery is reduced at rest.

Figure 9. Hypothetical analysis of the effects of exercise training. The diagram relating oxygen uptake and venous PO_2 used throughout this paper is again shown, and it is suggested that it can be used to analyze the improvement in maximum $\dot{V}O_2$ afforded by training. If a subject prior to training has a maximum oxygen uptake and mixed venous PO_2 indicated by point O, points A, B and C show three different ways in which a given increment in maximum oxygen uptake could be achieved.

Point A comes about with no change in tissue diffusing capacity, and only an augmentation in oxygen delivery. Point C represents the converse, namely, an increase in tissue diffusing capacity and no increase in oxygen delivery. Point B represents necessarily a combination of an increase in both tissue diffusing capacity and oxygen delivery. By assessing maximum oxygen uptake and mixed venous PO_2 before and after training, it should be possible to partition the improvement in oxygen uptake quantitatively into that component due to improvement in tissue diffusion capability and that due to augmented oxygen delivery.



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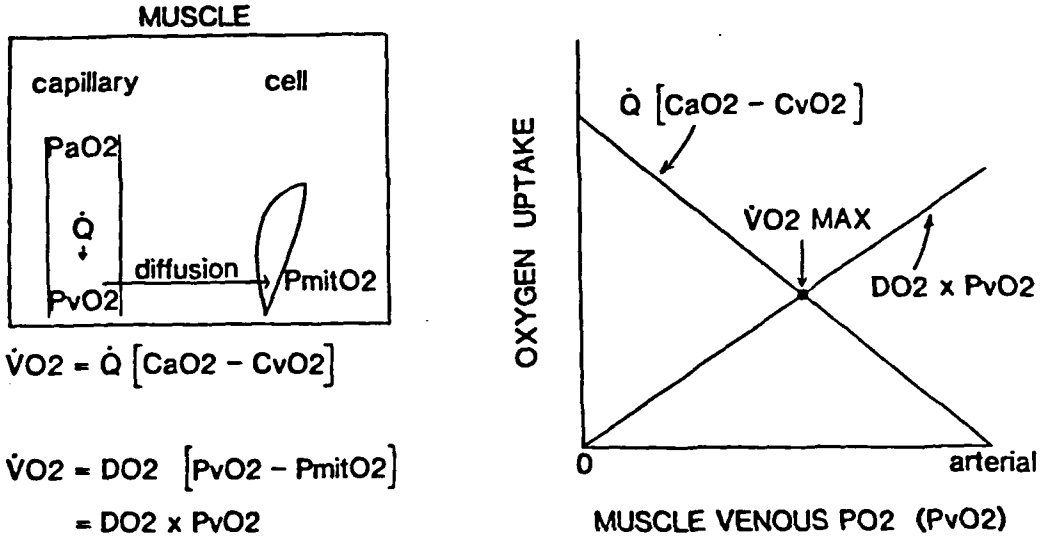

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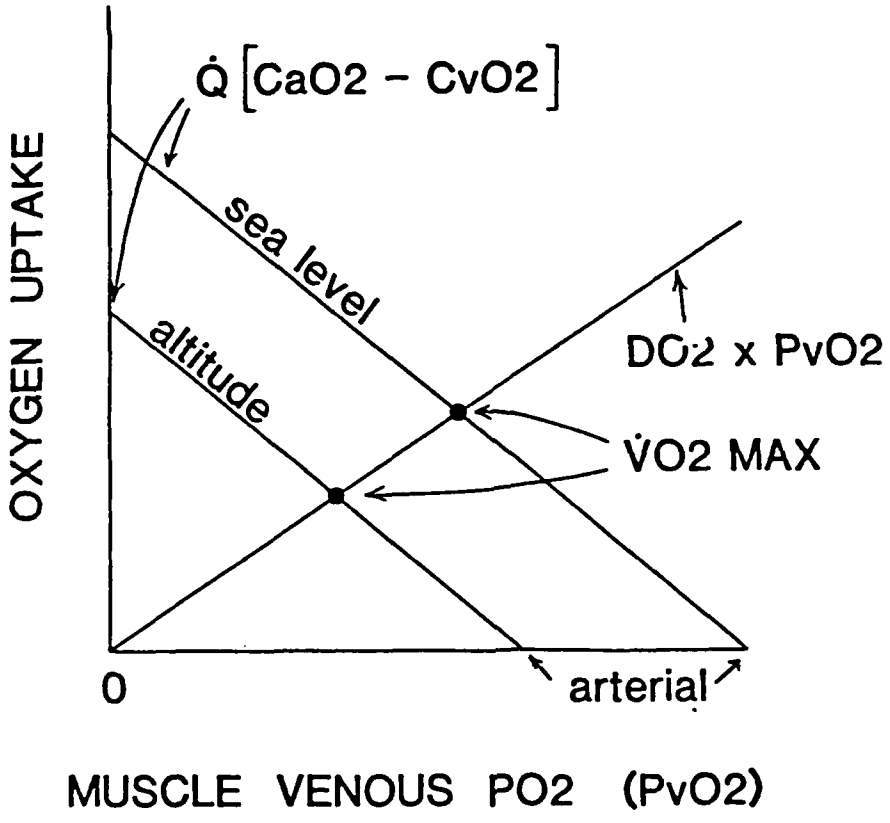

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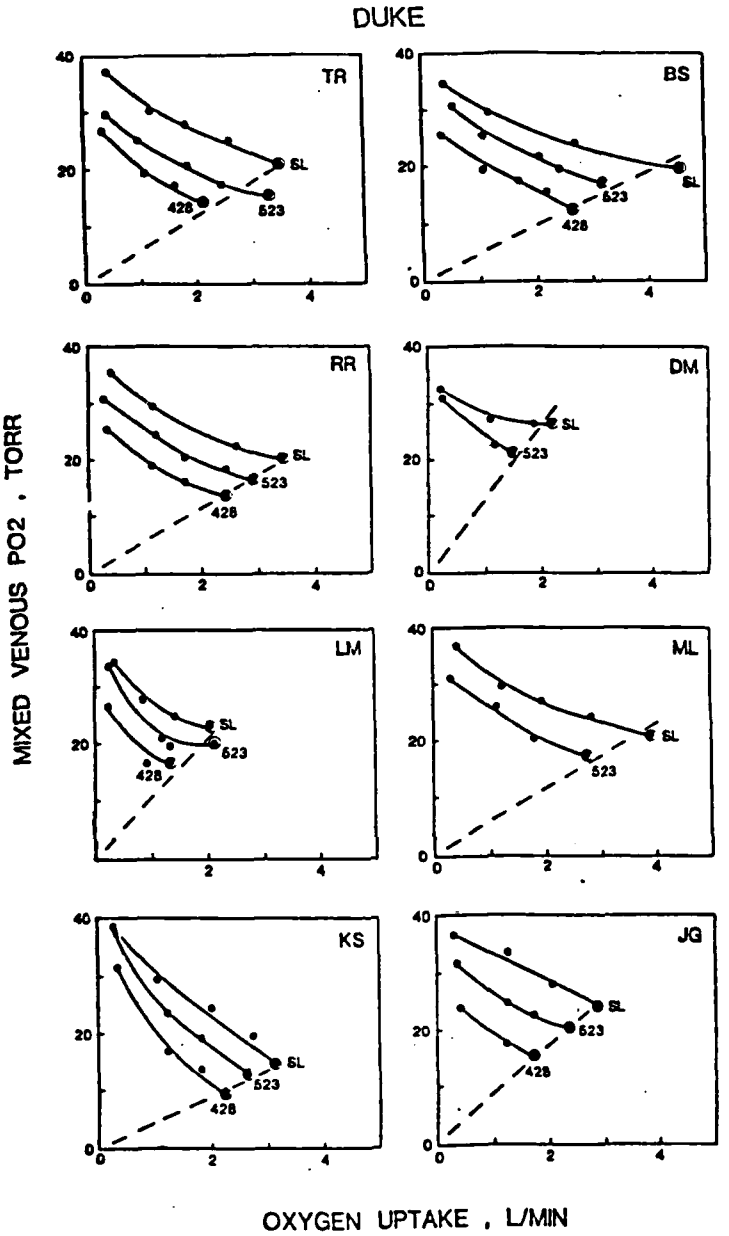

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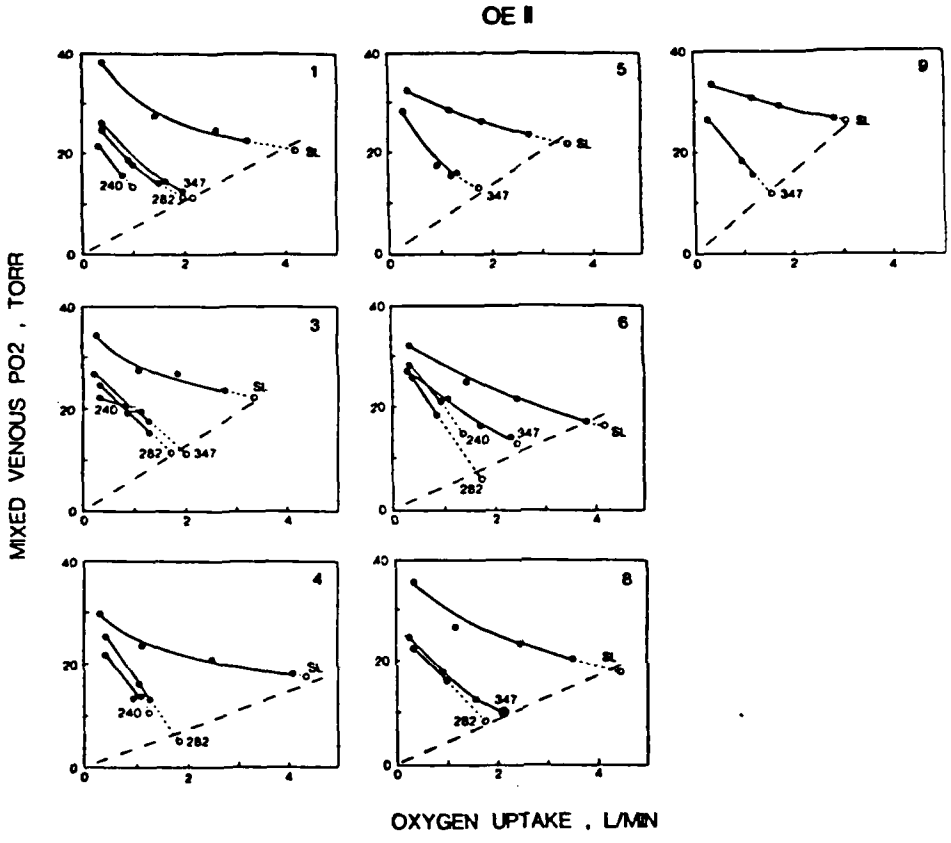

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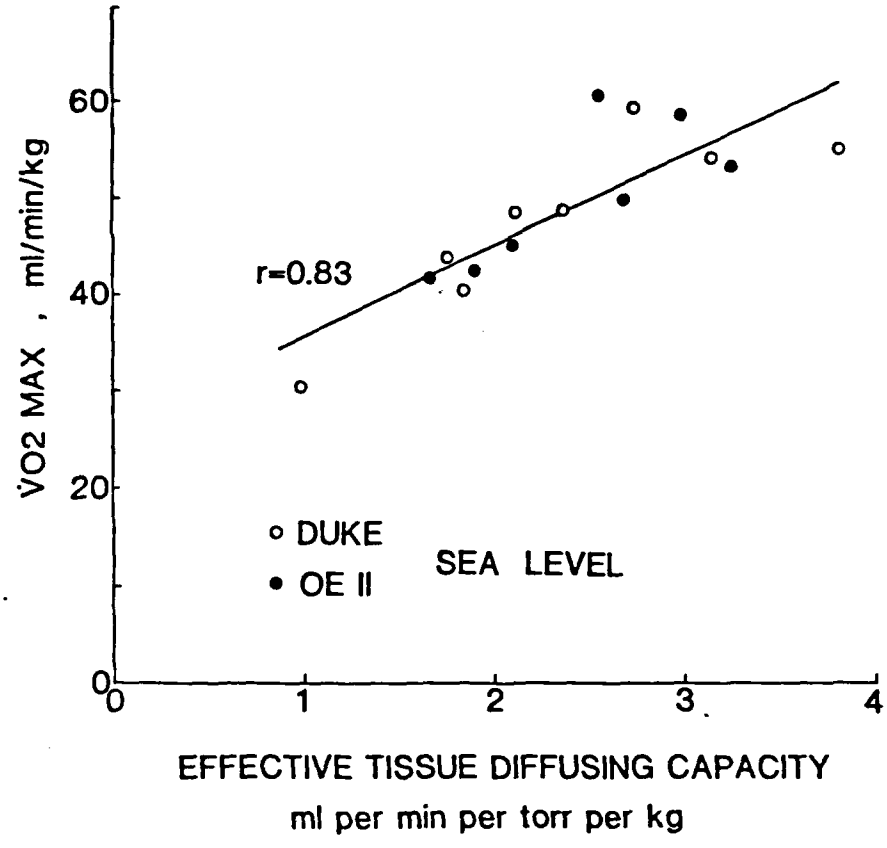

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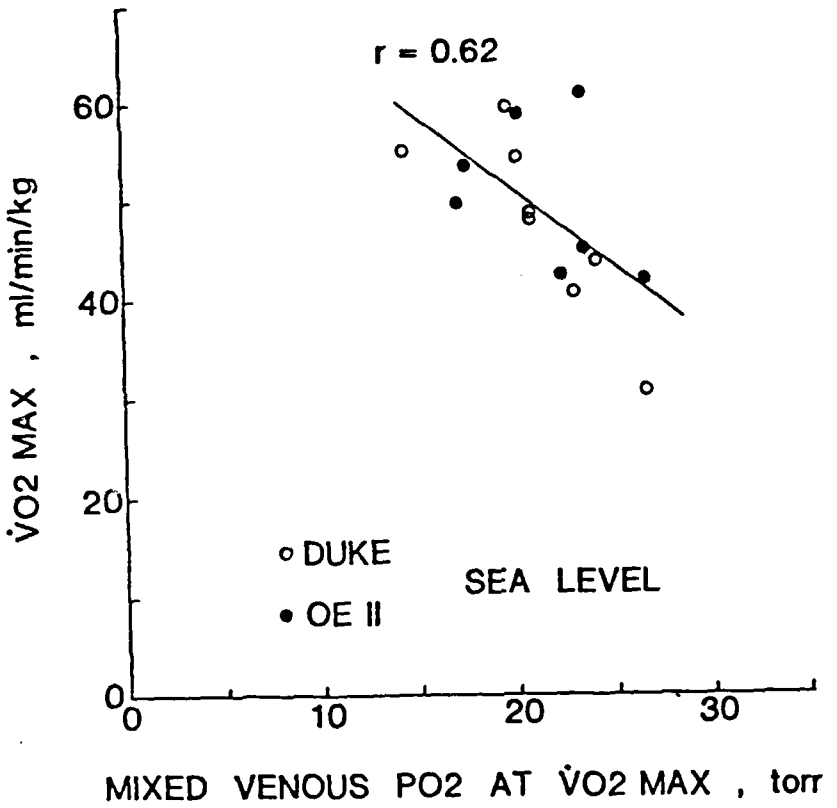

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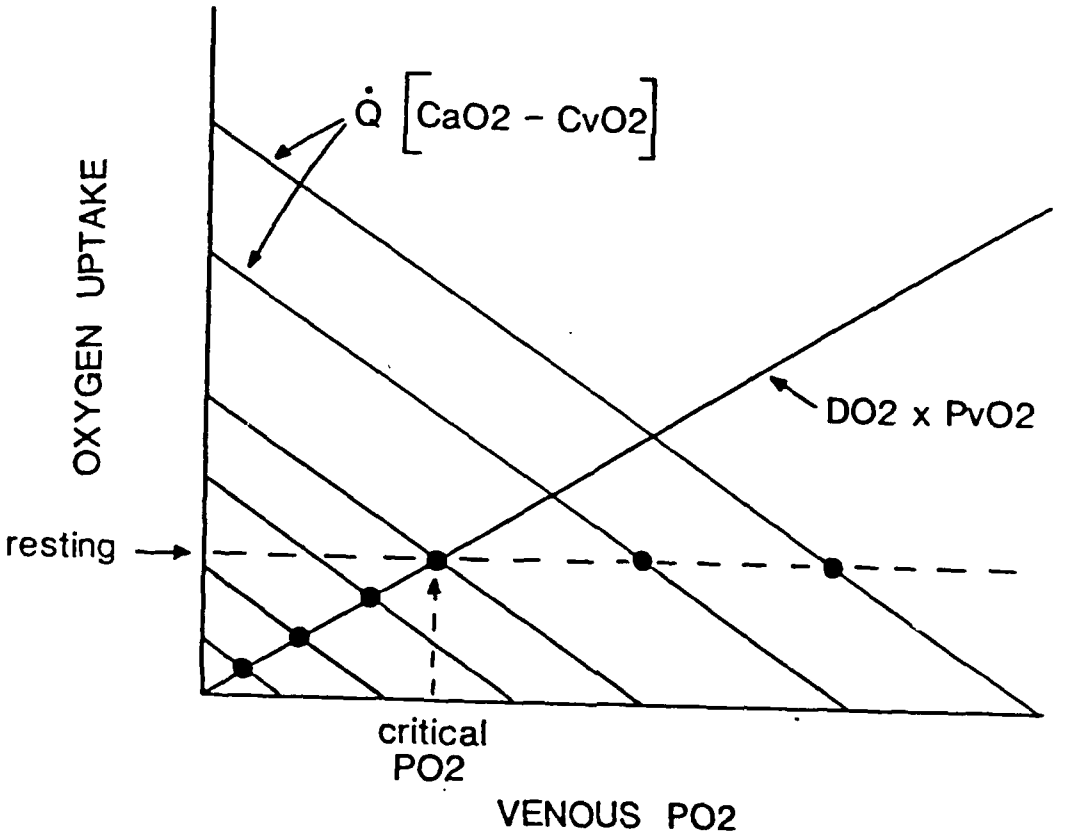

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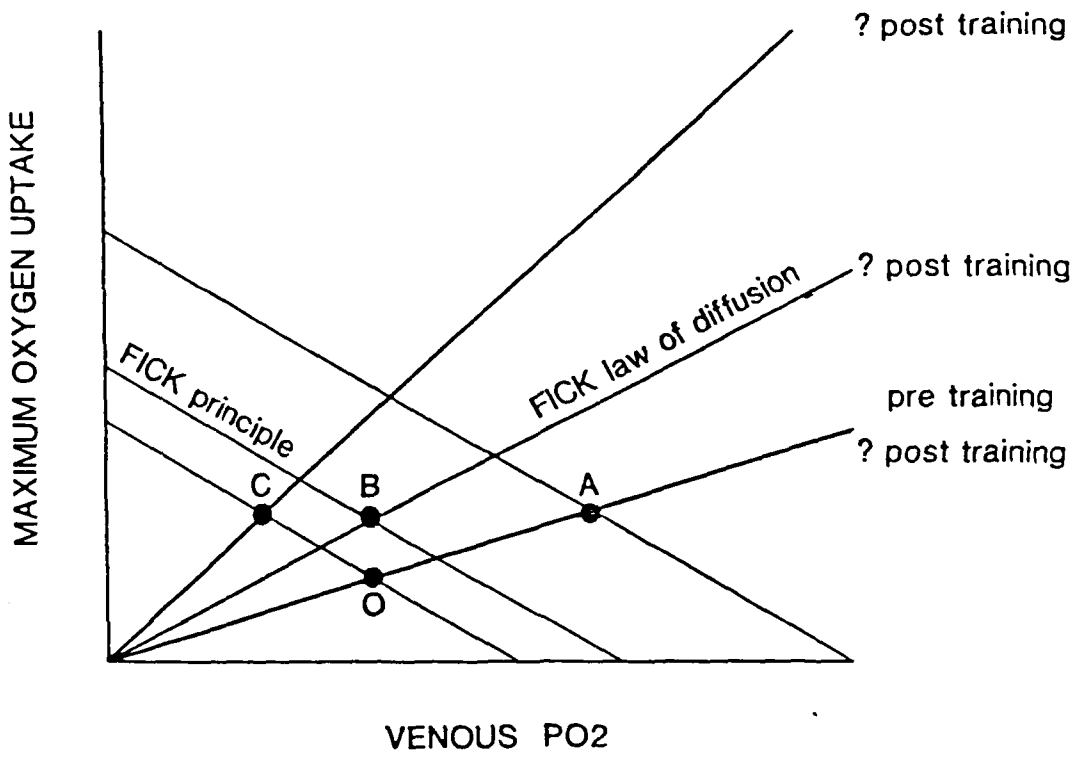

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